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HERITABLE DISORDERS OF CONNECTIVE TISSUE

I. The Clinical Behavior of Hereditary Syndromes

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INTRODUCTION

BECAUSE of the light they shed on normal mechanisms, many of the inherited ailments of man have importance far out of proportion to their numerical significance. Such is the case, at least potentially, with the hereditary disorders of connective tissue, the subject of these studies. This consideration, together with the increasing recognition of internal medical ramifications of these diseases, prompted this survey.

To be discussed are generalized hereditary disorders of connective tissue. Many local hereditary malformations and anomalies can be construed as heritable disorders of connective tissue. These will not be discussed, but rather attention will be concentrated on those heritable diseases which represent abnormality of a single element or biochemical mechanism of connective tissue wherever it is found throughout the body. These include the Marfan syndrome, the Ehlers-

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TABLE I. *HERITABLE DISORDERS OF CONNECTIVE TISSUE IN MAN. A SYNOPSIS OF SYMPTOMS*

DISORDERS	SKIN	JOINTS	EYE	BONE	BLOOD VESSELS	FASCIA	FUNDAMENTAL DEFECT
Ehlers-Danlos syndrome	Fragility; hyperelasticity	Hyperextensible	Ectopia lentis; microhemorrhages of retina		Dissecting aneurysm (?)	Eventration of diaphragm, hernia	Dystrophy of collagen? Overdevelopment of elastic fibers?
Pseudoxanthoma elasticum	Dystrophy in wear-and-tear areas		*Brück's membrane, crazing of:* angioid streaks	*Paget's disease*	*Peripheral arteries,* medial sclerosis *of:* hemorrhage		Dystrophy of collagen?
Osteogenesis imperfecta	Thin; abnormal scar formation	Hyperextensible	Sclera, thinning of: blue sclerotica	Brittle bones; otosclerosis (deafness)		Hernia	Maturation of collagen?
Marfan's syndrome		*Hyperextensible*	*Suspensory ligament of lens:* ectopia lentis	*Excessive length of long bones:* dolichostenomelia (long, thin extremities)	*Aortic media:* aneurysm	*Hernia*	*Defect of elastic tissue?*
Hurler's syndrome	Roughening	Limitation of mobility	Clouding of cornea	Dwarfism; dysostosis multiplex	Histologic infiltration	Hernia	Qualitative and/or quantitative abnormality of mucopolysaccharide formation?

Danlos syndrome, osteogenesis imperfecta, the Hurler syndrome, and pseudoxanthoma elasticum. On the basis of the information available, the nature of certain conditions—Paget's disease of bone, the Brailsford-Morquio syndrome, the Werner syndrome, calcinosis universalis, achondroplasia (chondrodystrophia fetalis), fibrositis (myositis) ossificans progressiva, familial systemic amyloidosis, and others—as possible generalized heritable disorders of connective tissue can only be speculated.

Heritable disorders of connective tissue will be discussed in the following order and under the following headings*:

I. The Clinical Behavior of Hereditary Syndromes.
II. The Biology of Normal Connective Tissue.
III. The Marfan Syndrome.
IV. The Ehlers-Danlos Syndrome.
V. Osteogenesis Imperfecta.
VI. Pseudoxanthoma Elasticum.
VII. The Hurler Syndrome.
VIII. Concluding Comments.

In Table I is presented the connective tissue areas in which clinically evident abnormalities occur in five of these syndromes. The underscored items indicate the predominant manifestations in the case of each. Overlap of manifestations is particularly noteworthy.

Certain features of the behavior of the hereditary syndromes discussed here are common to entities involving other tissues which share enzymatic mechanisms. The hereditary syndromes of connective tissue serve particularly well in demonstrating these features.

As stated above, the several disorders which will be discussed later are *generalized* abnormalities of connective tissue, although predominant presenting manifestations are likely to bring individual cases to the attention of specialists such as dermatologists, ophthalmologists, and orthopedists. Many students of hereditary disease syndromes were in the past preoccupied with germ layers. They were content if all components of a syndrome could be related to a single germ layer and were much perplexed when certain manifestations deviated from the single germ layer hypothesis. When it is appreciated that the abnormality involves one element of connective tissue wherever it is found, no perplexity is occasioned by the occurrence, for example, of ocular involvement in Marfan's syndrome, the other manifestations of which are clearly mesodermal in origin.

Some of the abnormalities resulting from these connective tissue disorders are not congenital malformations in the usual sense but have the nature of *abiotrophies*, the term suggested by Gowers[1] for neurologic disorders in which a tissue is capable of function for only a limited time because of an innate constitutional weakness. For instance, in pseudoxanthoma elasticum the characteristic skin changes are rarely discernible before the latter part of the second

*This series will appear in several successive issues of this JOURNAL. Since the articles are to be published in book form following completion of the series, reprints of individual articles will not be available.—EDITOR.

decade. Furthermore, wear and tear determine predominant localization of the skin lesions in the areas of flexion, of exposure to weather, of irritation by garments, and so on.

The complex clinical syndromes resulting from these disorders of connective tissue are in each instance the result of a *single* mutant *gene*, the action of which has wide repercussions because of its control of some basic biochemical process. The alternative possibility is that of gene linkage, i.e., that the major individual manifestations of a given syndrome are determined by separate genes located in close proximity on the same chromosome. The arguments for a single gene basis of these complex syndromes are as follows:

1. It is unlikely, although possible, that several genes would undergo mutation simultaneously to reproduce these syndromes again and again with such exactitude.

2. "Crossing-over" tends to separate linked characteristics so that in the course of a few generations there is no longer any particular association in a given individual. It is true that for closely neighboring genes the rate of "crossing-over" is so low that the relatively few human generations available to study may, in any one kinship, be inadequate to demonstrate separation of the components of a given syndrome. However, in the population at large, the situation is as stated by Snyder[2]:

> The occurrence of genetic linkage between the genes for two traits does not change the association for these traits in the population from what it would be if they were not linked. Stated conversely, a correlation between two traits in a free-breeding population does not indicate genetic linkage between the genes for these traits.

3. The most telling argument for a single-gene mechanism lies in the possibility of relating all manifestations of these multifaceted syndromes to a single fundamental defect. For example, in osteogenesis imperfecta, the manifestations in the skin, sclera, and bone can be related to a single defect, which may concern the maturation of collagen.[3] If it is possible to construct a convincing "pedigree of causes" relating all clinical manifestations of the syndrome to the basic defect in a descendant fashion, additional strong evidence for the single gene basis of the syndrome has been provided. Gruneberg[4] has constructed such a "pedigree of causes" for certain complex single gene syndromes of the mouse.

4. In both the mouse and the fruit fly there occur syndromes which have as diverse components as any which occur in man and which by more rigorous genetic tests than are possible in man appear to result from a single gene.[5]

"Pleiotropic" is the term customarily applied to these single genes which are responsible for complex syndromes. The implication is that one gene has several actions. It is likely that in fact the gene has but one action and that the apparent multiplicity of its effects is merely the result of the involvement in several processes of the single biochemical step which is controlled by the gene in question. In the strict sense, then, it may be that no gene is truly pleiotropic.

One occasionally hears statements such as, "That is one of these congenital-familial affairs with which anything can occur." It should not be necessary to emphasize the direct corollary of the single gene proposition: the clinical picture in each of these syndromes is as clear-cut and specific (with, of course, the clinical variability discussed below) as the clinical picture produced by a pathogenic microorganism. In many respects, hereditary disease differs from infectious disease only in that the etiologic agent is a mutant gene operating from within rather than a bacterium invading from without. The virologists have rather long been aware of the basic analogies between their field and that of the geneticist.[6] It is true that in the present state of our ignorance, it is impossible, in the case of some syndromes, to relate all components to a unitary biochemical anomaly. For example, in the syndrome of polyposis of the small intestine and melanin spots of the buccal mucosa, lips, and digits,[7] there is no obvious common denominator. Even in such a situation, however, the other arguments listed above make a single gene mechanism likely.

Wide *variability* in the clinical severity of the manifestations of these syndromes is the rule. This variability is demonstrated particularly dramatically by the syndrome of osteogenesis imperfecta (see later). By the geneticist the clinician's "degree of severity" is referred to as "expressivity." Penetrance, on the other hand, is an all-or-none affair. There will be fundamentally affected individuals in whom the manifestations are so mild that they do not deviate sufficiently from certain ones of the normal group to permit recognition as abnormal. These cases, the cases of incomplete penetrance, of *forme fruste*, correspond to the subclinical cases of infectious diseases. The familiar bell-shaped Gaussian curve probably accurately describes the distribution of cases as to severity (expressivity) (Fig. 1). The three vertical lines of the diagram indicate threshold of penetrance. These lines cross the distribution curve on the side constituted by cases of lesser grades of severity. At this end also the curve is overlapped by the normal distribution curve. The majority of recognizable cases are of intermediate severity; there are some very severe cases and some very mild ones. Those affected individuals in the zone of overlap have mild manifestations which, because of their occurrence as "normal variations" in a small proportion of the normal population, cannot be recognized as abnormal when the individual is studied. For the student of the individual, then, the threshold of penetrance is at the point of overlap of the two curves. A certain number of additional cases can be recognized by the student of the total genetic and clinical picture, by one who investigates the entire family in detail. (There are risks, of course, that some unaffected individuals will be incorrectly classified as affected.) It seems probable that when the basic defect in each of these syndromes is known and when a specific method for demonstrating the defect becomes available, all cases of each syndrome will be identifiable. At this point the threshold of penetrance will be moved back to the limit; and penetrance, an artificial concept at the best, will no longer have significance for these syndromes.

This wide variability in clinical expression is one basis for the phenomenon of "skipped generations" in these syndromes.

The variability in severity of manifestations is both interfamilial and intrafamilial. Interfamilial variability is greater, as a rule, than intrafamilial variability. Assuming that the basic biochemical defect is the same in all instances of a given syndrome, then the basis of variability must be sought in the rest of the genetic make-up of the individual. By and large the factors responsible for this variability are obscure. Occasionally, however, the influence of the genetic milieu on the expression of the mutant gene can be appreciated. For example, the characteristic skeletal changes of Marfan's syndrome tend to be partially submerged when the mutation occurs in pyknic stock; contrariwise, the skeletal changes may be particularly striking when the syndrome occurs in normally asthenic (dolichomorphic) stock.

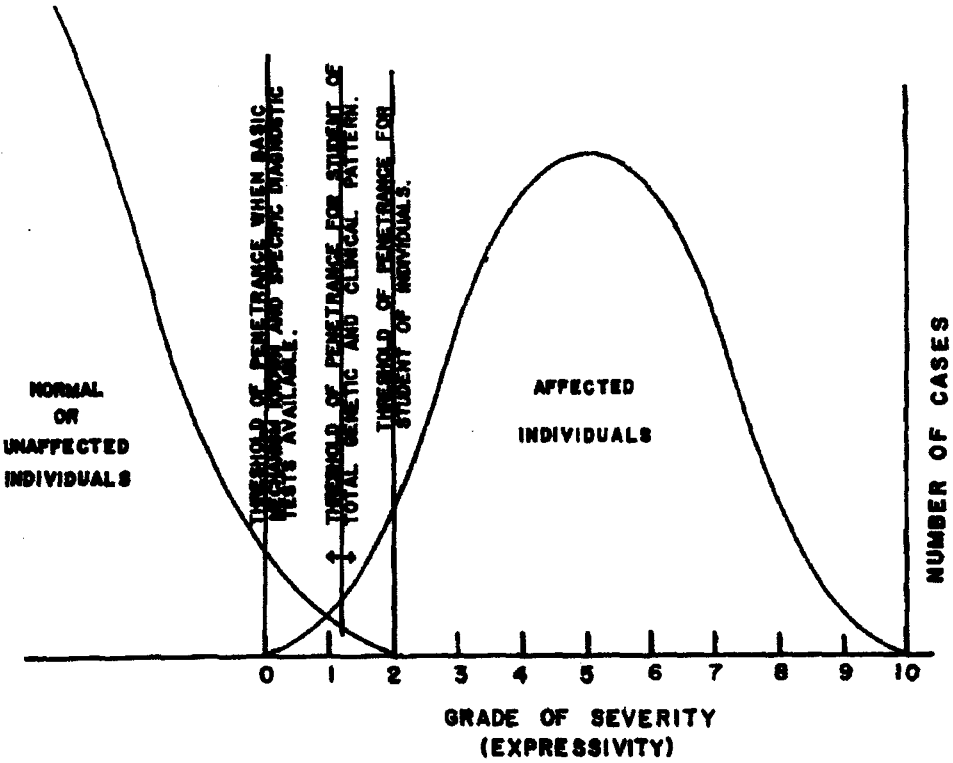

Fig. 1.—The interrelationship of penetrance and expressivity in hereditary syndromes. (See text.) (Inspired by Dr. H. Bentley Glass.)

The important influence of the genetic milieu is demonstrated by the fact that less variability of expression occurs within a family than does between members of different families. Furthermore, identical twins, identical in respect to their entire gene constitution as well as the mutant gene, usually show onset of symptoms at the same age and show manifestations of the same type and clinical severity.

The analogy between genetic and infectious disease has pertinence also in connection with the clinical variability of hereditary syndromes. As in infectious disease, host factors and host-parasite relationships are of great importance, the "parasite" in the case of genetic disease being the mutant gene, and the host factors mainly the genetic milieu in which mutant gene is operating.

It is a generalization with genetic disorders that wider variability occurs with "dominant" disorders than with "recessive" ones. The suggestion has been made[8] that natural selection tends to choose those genotypes in combination with which the deleterious mutant gene has less devastating effects. The result may be that in time the injurious effects become suppressed in the heterozygote and expressed only in the homozygote. When an hereditary disease has progressed to this stage in its biologic evolution, the disease trait will then display the genetic behavior termed "recessive."

The four disorders other than Hurler's syndrome which will be reviewed in detail display a *dominant* pattern of inheritance. Two features frequently displayed by recessive disease traits are not evident in these four syndromes: (1) a relatively high incidence of consanguinity in the group of parents of affected individuals; and (2) the occurrence of multiple cases in one sibship without involvement of other near relatives (a feature which often led recessive traits to be referred to as "familial"). Experience with other syndromes such as retinitis pigmentosa and Friedreich's ataxia[9] indicate that although the fundamental defect appears to be identical in the several instances (i.e., the "phenotype" is identical) the mode of inheritance may be "dominant" in one pedigree, "recessive" in another. This and the theoretically unstable, evolutionary state of dominance makes it necessary to scrutinize each pedigree individually.

Although the overwhelming majority of the pedigrees of Marfan's syndrome demonstrate a pattern consistent with a dominant mode of inheritance, in rare instances (see later) the inheritance may be recessive. It should not be necessary to point out that whether a disease is transmitted as a dominant or a recessive has no predictable bearing on the incidence of the disease trait in the population.

All cases of these syndromes either inherit the abnormality or fall victim thereto as a result of mutation of a gene regulating the normal biochemical counterpart of the basic defect. (Although the aberration of a normal gene or, as in the case of certain of the "inborn errors of metabolism," the loss of the active component of the gene is probably what occurs in mutation, it is now clear that in many instances mutation is a matter of position change; no alteration in the gene has occurred except one involving its position on the chromosome relative to its fellow genes.) All cases of these diseases have, of course, arisen by mutation in the more or less remote past. "Sporadic" is the designation employed clinically for those cases which occur as the result of *de novo* mutation during parental gametogenesis. The incidence of sporadic cases is inversely related to the care with which the families are studied. Because of the considerations diagrammatically indicated in Fig. 1, the incidence of sporadic (i.e., *de novo*) cases is always likely to be set abnormally high. All but one case in a family may be too mild to be identified positively as affected.

The term "heritable" was selected for the title of this review (rather than "inherited" or "hereditary") to express the fact that in a given individual the disease, although capable of being transmitted to the offspring, may not have been inherited, but rather have arisen by mutation. Since even in the latter instance, the abnormality occurs first in the germinal product of one or the other parent, it becomes a philosophical question whether the affected individual should be said to have inherited the trait or to have become affected at his earliest conception.

The factors responsible for the original mutation in these disorders are unknown.

The terms "genotype" and "phenotype" are used, respectively, to refer to the genetic constitution of the individual and to his physical, or somatic, makeup. "Phenocopies"—clinical syndromes, of either genetic or acquired origin, which at least superficially resemble the particular hereditary syndrome under investigation—may confuse clinical and genetic studies. For example, the fetal infection accompanying maternal rubella may so influence development that loose-jointedness, arachnodactyly, and ocular and cardiovascular anomalies—a picture superficially resembling Marfan's disease—result. Careful study of the precise type of eye or vascular involvement is necessary to exclude Marfan's syndrome in such instances. In many individual instances, the four syndromes which are the main topic of this review phenocopy each other, as is evident from Table I and as will be amplified below.

It is desirable to avoid eponyms wherever possible and it is preferable to employ designations which indicate as precisely as possible the fundamental nature of the disease entity under consideration. In the present state of our knowledge, however, there are good reasons to use eponyms for many syndromes: (1) Eponyms do not prejudice the search for the fundamental abnormality in each case. They do not conceal our ignorance of the basic defect. (2) By not using one feature of each complex syndrome as the designation, the eponym does not convey the impression that the presence of said feature is a sine qua non for the diagnosis, or that said feature occurs exclusively as a component of the particular syndrome. "Arachnodactyly" is a poor term for the Marfan disease because the fingers of many of the victims are no more spidery than those of many normal persons. Cutis hyperelastica and cutis laxa are poor terms for the Ehlers-Danlos syndrome since skin abnormalities may be relatively unimpressive in persons with striking joint hypermobility. The pity is not that eponyms are employed in these diseases but rather that there are no phonetically satisfactory or widely accepted eponyms to use in connection with disorders such as osteogenesis imperfecta and pseudoxanthoma elasticum, in which the defect is much broader in its localization than merely bone or skin, respectively.

Many individual manifestations occur in more than one of these syndromes resulting from defective connective tissue. For example: loose-jointedness with flat feet, pseudoclubfoot, habitual dislocation of joints, etc., may be a striking feature of the Marfan disease, the Ehlers-Danlos syndrome, and osteogenesis imperfecta. Hypotonicity and underdevelopment of skeletal musculature occur in the Marfan syndrome, osteogenesis imperfecta, and the Ehlers-Danlos syndrome. Impressively blue sclerae occur with Marfan's disease and, on the other hand, arachnodactyly occurs with osteogenesis imperfecta. Dissection of the aorta and ectopia lentis occur primarily in the Marfan syndrome but also occasionally in the Ehlers-Danlos syndrome. Because of this overlap as to individual components it is desirable, in the absence of a specifically descriptive title, to refer to these diseases by eponyms or by some relatively noncommittal name, rather than by a single manifestation which may be neither specific for the syndrome nor an invariable feature.

In summary, it may be pointed out that, as is dramatically illustrated by these hereditary disorders of connective tissue, one gene may have many effects. But, countrariwise, many different genes may individually or in combination produce a particular abnormal trait. The resulting complexities of clinicogenetic analysis are apparent.

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